Results of a Long-Term Postmarketing Case Series Study of Adult Osteosarcoma and Teriparatide in the US

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CONFLICT OF INTEREST

K. Midkiff, D. Harris, A. Gilsenan, D. McSorley, and E. Andrews are employees of RTI Health Solutions, which received funding from Eli Lilly & Co. to conduct this study. The contract between RTI Health Solutions and the sponsor includes independent publication rights. N. Kellier-Steele is a full-time employee of Eli Lilly & Co., the study sponsor, and holds stock in Eli Lilly & Co.

BACKGROUND

- Forteo® (teriparatide) is a recombinant human parathyroid hormone analog (1-34),[rhPTH(1-34)] indicated for:
  - Treatment of postmenopausal women with osteoporosis at high risk for fracture
  - Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture
  - Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture
- In preclinical studies in rats, teriparatide caused a dose-dependent increase in the incidence of osteosarcoma.
- Osteosarcoma is a rare bone cancer in humans. The background incidence for adults aged 40 and older[1] standardized to the age-sex distribution of patients receiving teriparatide[2] is 3.2 cases per million population per year.
- As a condition of approval, the Food and Drug Administration requested that this postapproval surveillance study be conducted.[3,4]

OBJECTIVES

- Primary: (1) to identify incident cases of osteosarcoma, if any, with a history of treatment with teriparatide; and (2) to identify and interview 33% of newly diagnosed cases of osteosarcoma in adults aged 40 years and older in the United States (US)
- Secondary: To systematically collect, for descriptive epidemiology purposes, additional patient information, including demographics and data related to other risk factors for osteosarcoma

METHODS

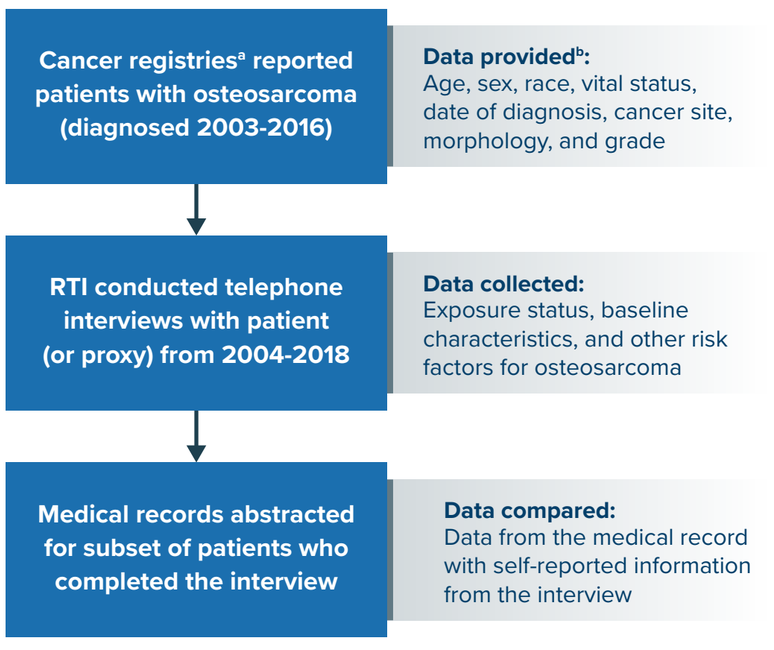
Study Design

- Retrospective case series

Eligibility Criteria

- Adults aged 40 and older at the time of osteosarcoma diagnosis on or after January 1, 2003, in the US

Figure 1. Data Collection



[a] Cancer reporting is mandatory in all US states, and cancer registries collect cancer diagnoses for 97% of the US population.[5]

[b] Deidentified data was provided for all osteosarcoma cases captured by participating registries. Identifiable data was provided to RTI only after permission requirements were fulfilled.

Analysis

Main Analysis

- Standardized incidence ratio (SIR) and corresponding 90% confidence interval (CI) where **SIR = D/E; D** = observed number of patients with osteosarcoma reporting teriparatide use, and **E** = the expected number of osteosarcoma cases among teriparatide users captured by the study.[a]

[a] The expected number was estimated by the product of the OS background incidence rate, the estimated person-time at risk following exposure to teriparatide since drug launch, and the study interview rate.

Sensitivity Analyses

- **D** was increased by including other cancers where misclassification with osteosarcoma was possible.[b]
- **E** was recalculated for a variety of plausible alternative values for its constituent components: (1) the background incidence rate of OS, (2) the estimated person-years at risk, and (3) the estimated interview rate obtained in the surveillance study.

[b] Five additional similar cancers where the primary site was bone.

Secondary Analysis

- Mean and percentage of patients with specified demographic and other characteristics were calculated.

Other Analysis

- Age at diagnosis, site, and morphology of tumor were compared for all patients reported by cancer registries and those with completed interviews.
- Percentage agreement for information collected via telephone and information abstracted from medical records was calculated.

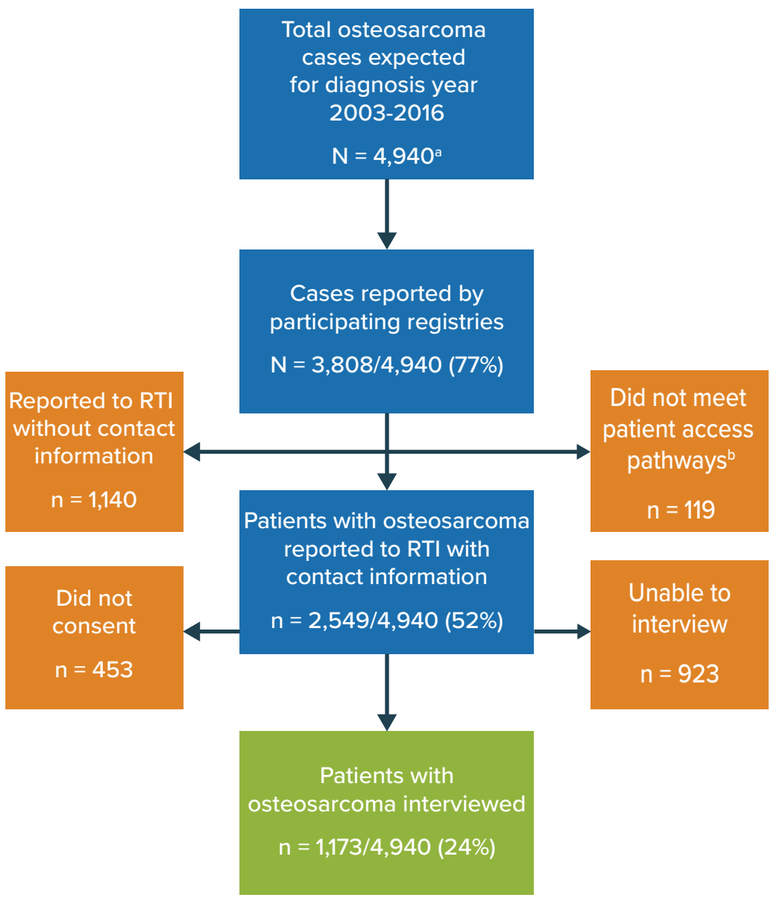
RESULTS

- Interviews were completed for 1,173 patients from an estimated total of 4,940 cases in the US (24% interview rate) (Figure 2), and the questionnaire response rate was 46% (1,173/2,549).
- 30 cancer registries participated in the study.
- The person-years at risk were estimated to be 5,432,764.

Main and Sensivity Analysis Results

- Three patients reported a prior history of teriparatide treatment that was confirmed, and the expected number of cases was 4.2, yielding an SIR of 0.7 (90% CI, 0.2-1.9).
- Varying the number of observed and expected cases did not produce a 90% lower confidence bound that exceeded 1.0 (Figure 3).

Figure 2. Study Accrual for Patients Diagnosed From 2003 to 2016



[a] Estimated using the Surveillance, Epidemiology, and End Results rate of osteosarcoma: 2.5 per million population per year applied to Annual Estimates of the Resident Population by Age and Sex for States from 2003 to 2016.

[b] Varying requirements among registries that had to be met before RTI could contact patients to conduct the telephone interview.

Secondary Results

- Most patients were white (84%), non-Hispanic (79%), and there were slightly more males (53%) than females.
- The mean age at osteosarcoma diagnosis was 61 years.
- The prevalence of known risk factors for development of osteosarcoma was 19% for history of radiation and 4% for history of Paget's disease of bone.
- The distribution of other characteristics reported during the telephone interview are shown in Table 1.

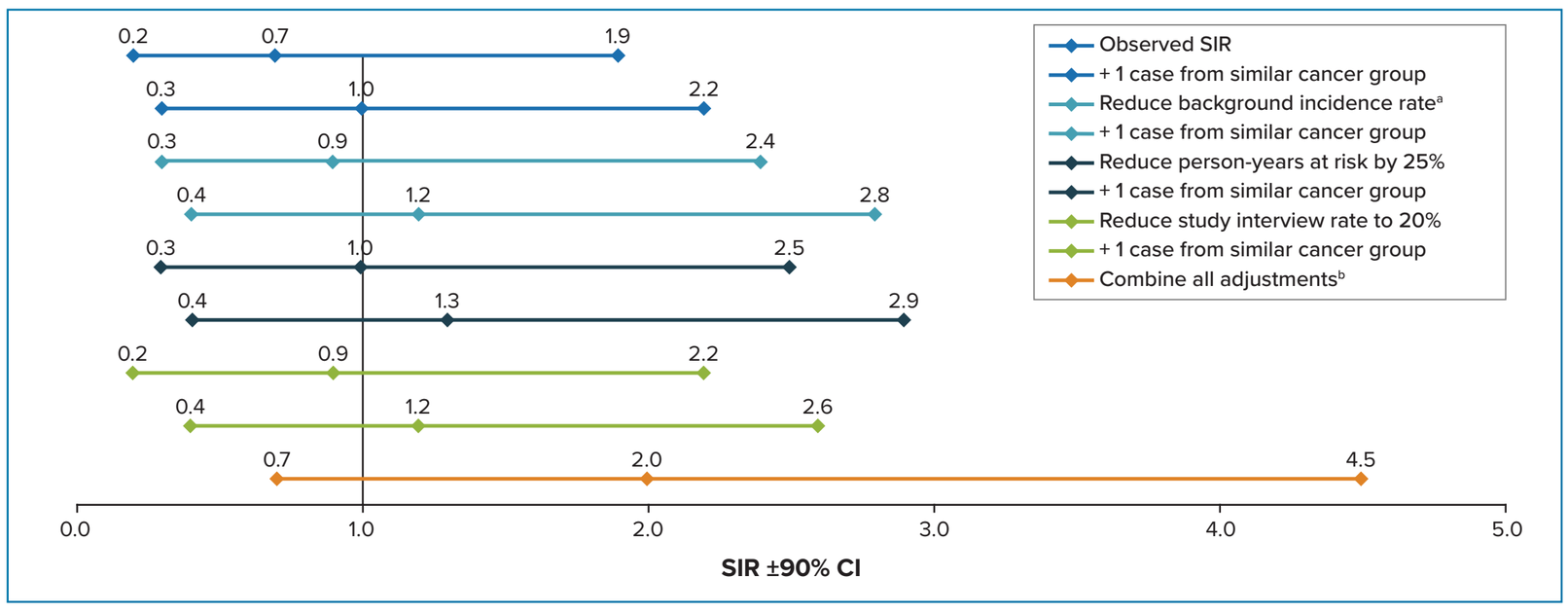
Table 1. Self-Reported Prevalence of Exposures (and Characteristics) Among Interviewed Patients and Proxies (N = 1,173)

Exposure/Characteristic	n (%)
Lifestyle exposures	
Drank alcohol during 12 the months before diagnosis	736 (63)
Smoked ≥ 100 cigarettes in their lifetime	577 (49)
Treatment, injury, and infection exposures	
Previous injury or infection at tumor site	181 (15)
Prior radiation treatment	226 (19)
Environmental exposures	
Agricultural pesticide exposure	277 (24)
Occupational petrochemical exposure	141 (12)
Occupational radiation exposure	80 (7)
Personal and family medical history	
Personal history of other cancers	314 (27)
Family history of osteosarcoma	52 (4)
Personal history of Paget's disease of bone	46 (4)

Assessment of Bias

- There were no notable differences in age (Figure 4), site or type of tumor between all patients reported in a de-identified manner and patients for whom interviews were completed.
- Agreement was high between the telephone interview responses and medical record data when comparing:
  - Osteoporosis medications (96% or higher, except Fosamax [92%])
  - History of osteoporosis (85%)
  - History of radiation therapy or chemotherapy treatment or history of prior cancer (89%)
  - History of Paget's disease (97%)

Figure 3. Sensitivity Analyses of the Standardized Incidence Ratio

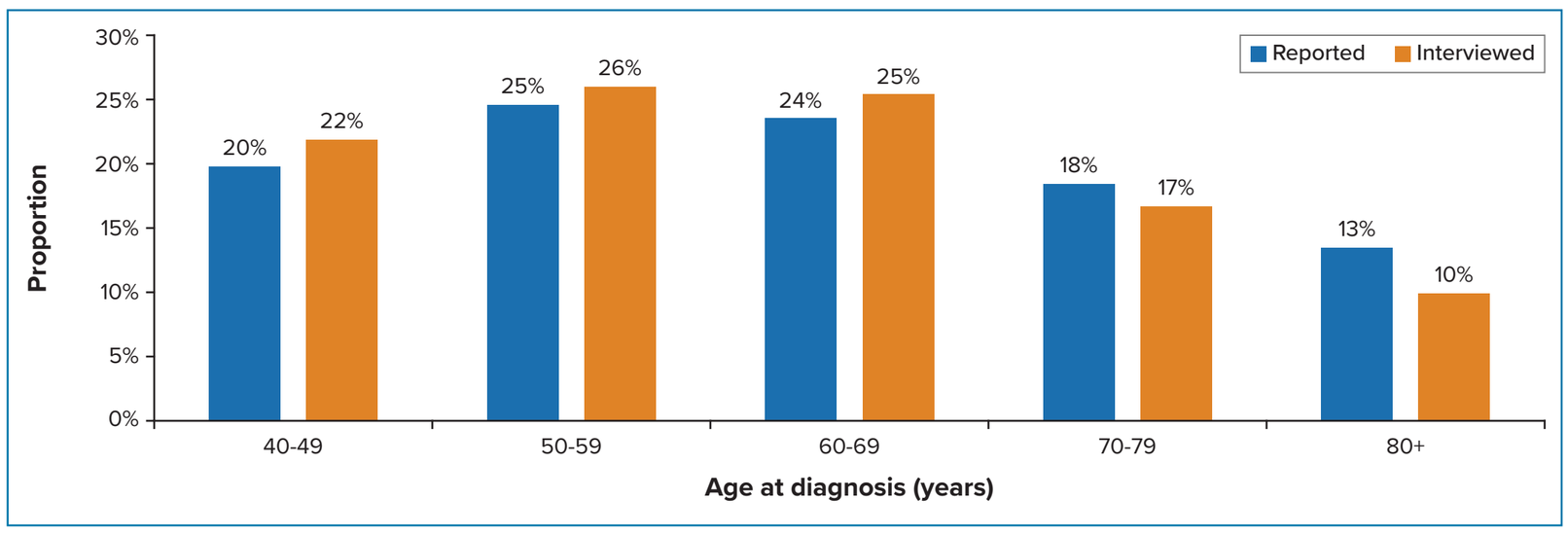


Note: +1 case from similar cancer group = chondrosarcoma.

[a] The background incidence rate was reduced from 3.2 cases per million population per year to 2.5 cases per million population per year.

[b] Combine all adjustments included decreasing the person-years at risk by 25%, reducing the study interview rate to 20%, including the chondrosarcoma case and reducing the background incidence rate to 2.5 cases per million population per year.

Figure 4. Distribution of Age at Diagnosis for Completed Interviews (N = 1,173) Versus All Patients Reported by Registries (N = 3,808)



DISCUSSION AND CONCLUSIONS

- The study results provide evidence that there is not an increased risk of osteosarcoma among adults receiving teriparatide in the US and suggest any potential increase would be small.
- These results should be helpful to clinicians as they weigh possible risks against potential benefits of treating patients with osteoporosis at high risk for fracture.

REFERENCES

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Presented at: 35th International Conference on Pharmacoepidemiology & Therapeutic Risk Management; August 24-28, 2019; Philadelphia, PA